

Utah Medicaid Pharmacy and Therapeutics Committee

Therapeutic Options for Spinal Muscular Atrophy

P&T Presentation: September 2019

Review prepared by:
Mohit B. Bhakta, Pharm.D.

Contents

Introduction.....	3
Diagnosis.....	3
Disease Types and Disease Severity.....	3
Clinical Guidelines.....	4
Pharmaceutical Therapies	4
Approved Indications	4
Clinical Pharmacology	5
Dosage and Strength Availability	5
Adverse Events.....	5
Therapeutic Efficacy	7
Summary and Recommendation	12
References	13

Introduction

Spinal Muscular Atrophy (SMA) is a rare autosomal recessive disorder, meaning two SMN1 copies have mutations or missing for SMA to develop, that causes weakness and wasting in voluntary muscles of infants, children, and more rarely, in adults.¹ This rare heritable disorder occurs one in every 10,000 births or an estimated 500 new SMA cases per year.¹

SMA is classified into five types based upon age of symptom onset and motor function achieved. SMA severity presents on a spectrum with Type 0 being the most severe and Type IV being less severe based upon a combination of clinical characteristics and the number of SMN2 copies present.² Most cases this disorder is caused by a homozygous mutation located on the SMN1 gene that results in SMN protein deficiency.² Disease severity is inversely related to the number of partially functional gene, SMN2, copies present; greater number of SMN2 copies present is associated with milder disease.

Diagnosis

Any infant with unexplained muscle weakness, hypotonia, or any additional cues in children or adults include: hyporeflexia or areflexia, loss of motor skills, tongue fasciculations.¹ Molecular genetic testing with mutation analysis can confirm SMA diagnosis.^{1,3} Other diagnostic methods include, magnetic resonance imaging and muscle biopsy. Differential diagnosis varies based upon age of symptom onset and motor function, seen in table 1.^{1,4}

Disease Types and Disease Severity

As mentioned previously, disease severity is inverse to SMA type, type 0 being the most severe. SMA type 0 is also known as prenatal onset SMA.^{1,4} Since the child is affected in the womb, this may lead to a life expectancy less than a year.^{1,4} SMA characteristics are present prior to birth, which leads to fetus being less active within womb. After birth, child's ability to breathe, swallow, and move are significantly reduced when compared to healthy newborns.⁴

SMA Type	Age of Onset	Predicted Number of SMN2 Copies Present	Highest Motor Function Achieved	Life Expectancy
0	Prenatal	1	None	<6 months
1	0 – 6 months	2	Sit with support only	<2 years
2	<18 months	3	Sit independently	10 – 40 years
3	>18 months	3 – 4	Walk independently	Normal Lifespan
4	>21 years	>4	All motor milestones achieved with mild weakness	Normal Lifespan

Table 1: SMA Disorder Type & Motor Function

For SMA type 1 or infantile onset, SMA symptoms appear at birth or within first few months of life.^{1,4} These newborns typically have generalized muscle weakness, breathing distress, weak cry, difficulty swallowing, etc.⁴ As a result of such early symptom onset, these newborns may not reach developmental milestones and have a life expectancy of less than 2 years.⁴

For SMA type 2 or intermediate SMA, symptoms usually appear between months 7 through 18.^{1,4} With the disorder onset slightly later than the previously mentioned SMA types, the newborns may sit up

without assistance and may reach other developmental milestones.⁴ These individuals have a life expectancy of 10 to 40 years.¹

For SMA type 3 or Kugelberg Welander disease, symptom onset usually occurs between 2 to 17 years of life.^{1,4} The child will likely achieve a large portion of developmental milestones but may have difficulty running, getting in and out of chairs, climbing stairs, etc.^{1,4} Later in life, these individuals may lose ability to ambulate and may require a wheelchair.⁴

For SMA type 4 or adult-onset SMA, symptoms appear usually after 30 years.^{1,4} This SMA type results in muscle tremors, twitches, mild muscle weakness in the legs that may progress to upper limbs with time.^{1,4} These affected individuals should meet all developmental milestones and a small number of patients may require wheelchair assistance as time progresses.⁴

Clinical Guidelines

The International Conference of the Standard of Care for SMA published a consensus statement surrounding the standard of care for SMA patients which was released in 2007.⁵ With advancements in technology and recent approval of the first SMA drug, there has been an updated consensus statement release in 2017 by the European Neuro Muscular Centre (ENMC).⁵ This was a two-part update covering previously discussed topics.

Section 2.1. SMA Diagnosis, the ENMC agreed the gold standard of SMA diagnosis is through molecular genetic testing of both, SMN1 and SMN2.⁵ The following methods are preferred: multiplex ligation dependent probe amplification (MLPA), next generation sequencing (NGS), or quantitative polymerase chain reaction (qPCR).⁵ Obtaining values for both, SMN1 and SMN2, copies are relevant in identifying deletions, disorder prognosis, and possible therapeutic approaches.⁵

Focusing on *Section 7: Medications, Supplements, and Immunizations*, a Cochrane review, published in 2012, reported six randomized placebo-controlled trials using various treatments for SMA.⁶ SMA treatments mentioned were the following: creatine, thyrotropin-releasing hormone, phenylbutyrate, hydroxyurea, gabapentin, and combination use of acetyl-L-carnitine and valproate.⁶ None of the clinical trials demonstrated statistically significant effects on outcomes in participants with SMA type 2 or type 3. Unfortunately, the consensus update was finalized prior to any drugs completing the regulatory process and becoming commercially available.⁶ With the next update, yet to be announced, there is hope that the standard of care will include the newly approved medications, Spinraza® and Zolgensma®, and any other approved treatments.

Pharmaceutical Therapies

Approved Indications

Currently, there are two disease-modifying therapies approved by the Food and Drug Administration (FDA), Spinraza® (nusinersen) and Zolgensma® (onasemnogene abeparvovec-xioi). Biogen Idec's Spinraza® was approved in December 2016 making it the first drug to market. Spinraza® is a modified antisense oligonucleotide indicated to treat SMA in pediatric and adult population.⁷ Novartis/AveXis's Zolgensma® was approved in May 2019 for a more specific SMA population, pediatric patients less than 2 years of age with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene. Zolgensma® is an adeno-associated viral vector-based gene therapy.⁷

Drug	Approved Indication
Spinraza®	SMA in pediatric and adult patients.
Zolgensma®	SMA in patients less than 2 years of age with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene

Table 2: SMA Drugs and FDA Approved Indications

Clinical Pharmacology

SMA is caused by a mutation in chromosome 5q which leads to inefficient SMN protein production. Spinraza® is designed to increase expression of exon 7 inclusion in the SMN2 messenger ribonucleic acid (mRNA). Upregulating the expression results in an increase production of SMN protein.⁸ Zolgensma® mechanism of action is different by delivering a functional gene copy of the human SMN protein to replace the defective SMN1 gene.⁹ Through cell transduction, transcription and expression of SMN protein is increased. By ultimately increasing the deficient SMN protein, the disease severity is lessened.⁹

Dosage and Strength Availability

Spinraza® is available in a 12 mg/5 mL (2.4 mg/mL) injection administered via intrathecally. To initiate therapy, the patient is given four loading doses at different intervals. Whether a loading dose or maintenance dose, each dose given to the patient is one vial, 12 mg/5 mL.⁸ The first three loading doses should be administered 14-days apart and the 4th loading dose should be administered 30 days after the 3rd loading dose.⁸ After completing the first four loading dose, the patient is then given a maintenance dose every four months life long.⁸

Zolgensma® is one-time treatment option that is available as treatment kits tailored to patient's weight, in kilograms.⁹ Based on the patient's weight, the patient will receive 1.1×10^{14} vector genomes per kilogram (vg/kg) of body weight. 24 hours prior to administering Zolgensma®, the patient must receive systemic corticosteroids.⁹ After the corticosteroid therapy, the patient will receive a one-time slow intravenous infusion.⁹ Upon completion, the patient's platelet count, liver function, and troponin-1 are routinely monitored up to three to five months.⁹

Adverse Events

Summary:

Based on multiple clinical trials, common adverse events reported were pyrexia, constipation, and respiratory related events including respiratory infections.^{8,9} The tables below include reported adverse events from clinical trials for both pharmacologic agents.

Monitoring:

Monitoring to assess safety should include comparative assessments of baseline lab values and labs drawn prior to each dose: liver function test, platelet count, coagulation laboratory testing, quantitative urine protein testing.^{8,9} For Zolgensma®, it is imperative to obtain baseline anti-AAV9 antibody testing prior to initiating therapy for efficacy and assessment of troponin-1 levels to ensure levels return to baseline.⁹

Adverse Events	Reported Incidence in Trials (%)	
	Spinraza®	Sham Procedure (Control group)
N	80	41
Any adverse event	96	98
Pyrexia	56	59
Constipation	35	22
Upper respiratory tract infection	30	22
Pneumonia	29	17
Respiratory distress	26	29
Respiratory failure	25	39
Atelectasis	22	29
Vomiting	18	20
Acute respiratory failure	14	24
Gastroesophageal reflux disease	12	20
Decreased oxygen saturation	12	24
Cough	11	20
Dysphagia	11	22

Table 3: Adverse Events Observed in ENDEAR Clinical Trial¹⁰

Adverse Events	Reported Incidence in Trials (%)	
	Spinraza®	Sham Procedure (Control group)
N	84	42
Any adverse event	93	100
Pyrexia	43	46
Upper respiratory tract infection	30	45
Headache	29	7
Vomiting	29	7
Back pain	25	0
Cough	25	21
Nasopharyngitis	24	36
<i>Serious adverse events with the highest incidence</i>		
Pneumonia	2	14
Influenza	0	5
Respiratory distress	2	5
Fecaloma	0	5
Dehydration	0	5

Table 4: Adverse Events Observed in CHERISH Clinical Trial¹¹

Adverse Events	Reported Incidence in Trials (%)	
	Spinraza®	Sham Procedure (Control group)
N	21	NR*

Total number of serious adverse events reported	50	NR*
Acute respiratory	8	NR*
Pneumonia	14	NR*
Respiratory distress	12	NR*
Respiratory failure	6	NR*
Respiratory syncytial virus infection	6	NR*
Respiratory tract infection	6	NR*
Rhinovirus infection	8	NR*
<i>Additional serious adverse events of special interest, (%)</i>		
Bronchiolitis	2	NR*
Lower respiratory tract infection	2	NR*
Parainfluenzae virus infection	2	NR*
Pneumonia (aspiration)	4	NR*

Table 5: Progress Report of Adverse Events Observed in EMBRACE Clinical Trial; *NR= Not Reported ¹²

Adverse Events	Reported Incidence in Trials (%)	
	Low-dose scAAV9	High-dose scAAV9
N	3	12
Any serious adverse event reported	100	83
Adverse event associated with treatment	33	25
Upper respiratory tract infection	33	83
Vomiting	0	67
Constipation	33	58
Pyrexia	33	50
Gastroesophageal reflux	33	42
Pneumonia	0	42
Rhinovirus Infection	33	33
Cough	0	42
Elevated aminotransferase level	33	25
Respiratory failure	33	25
Parainfluenza virus infection	33	25

Table 6: Adverse Events Observed in START Clinical Trial ¹³

Therapeutic Efficacy

The following two gene therapies have been studied in a variety of settings, although not compared to one another, thus limiting the ability to compare head-to-head therapy efficacy. Below are the compiled evidence tables from monotherapy trials. ¹¹⁻¹⁷

Ref.	Drug Regimens	n	Time	Demographics	Design	End Points	Results/Comments				
Spinraza® Clinical Trials											
10. ENDEAR Clinical trial	1. Nusinersen (Spinraza®) <ul style="list-style-type: none">Dose was adjusted according to estimated cerebrospinal fluid for the infant's age on the day of dosingDoses were administered on days 1, 15, 29, and 64. Maintenance doses were given on days 183 and 302 2. Sham procedure (control group) <ul style="list-style-type: none">Procedure consisted of a small needle prick of a lumbar-puncture injectionSham procedures were administered on same dosing schedule as nusinersen treatment group	122	Preplanned interim analysis occurred day 183 of involvement. Due to study meeting primary end-points, study was terminated and all infants were transferred into an open-label extension study, SHINE	Inclusion: <ul style="list-style-type: none">Confirmed diagnosis of SMA through genetic testingTwo copies of SMN2 geneGestational age between 37 to 42 weeks<6 months of age at SMA symptom onset<7 months of age upon screening	RCT, PC, DB, PA, ITT	Two primary efficacy end points: 1. Motor-milestone response defined by Hammersmith Infant Neurological Examination (HINE) a. Motor-milestone response occurred when infant met the following two criteria: 1) improvement in at least one listed category OR have more improvement in categories compared to worsening categories 2. Event-free survival that is defined as the time to death or the use of permanent assisted ventilation There were 6 secondary endpoints: CHOP INTEND response, no death, no use of permanent assisted ventilation, compound muscle action potential (CMAP) response, no death or use of permanent assisted ventilation among those with disease duration of ≤13.1 weeks at screening or >13.1 weeks at screening	Primary End Point Motor-milestone response <ul style="list-style-type: none">Interim analysisFinal analysis No death or use of permanent assisted ventilation Based on the interim analysis, a significant number of infants belonging to the nusinersen group had motor-milestone response, 41% vs. 0%. Based upon these results, the ENDEAR trial was terminated early and infants were evaluated at end-of-trail visits. After final evaluation, infants were transferred to the SHINE trial, open-label extension study.	Nusinersen Group (%) 21/51 (41) 37/73 (51) 49/80 (61)	Control Group (%) 0/27 0/37 13/41 (32)	Hazard Ratio (95% CI) 0.53 (0.32-0.89)	P-Value 0.005
11. CHERISH Clinical trial	1. Nusinersen (Spinraza®) <ul style="list-style-type: none">Dose was adjusted according to estimated cerebrospinal fluid for the infant's age on the day of dosingDoses were administered on days 1, 29, and 85Maintenance dose was given on day 274 2. Sham procedure (control group) <ul style="list-style-type: none">Procedure consisted of a small needle prick of a lumbar-puncture injectionSham procedures were administered on same dosing schedule as nusinersen treatment group	126	Trial length 15 months	Inclusion: <ul style="list-style-type: none">Confirmed diagnosis of SMA through genetic testing verifying 5q SMA (homozygous deletion, mutation, or compound heterozygote in SMN1)Symptom onset after 6 months of agePresence of the following features at screening: an age of 2 to 12 years, ability to sit independently, no history of the ability to walk independently, and HFMSE score of 10 to 54.	DB, PC, Phase 3	Primary end point: <ul style="list-style-type: none">Least-square mean change from baseline in the total HFMSE score at 15 months<ul style="list-style-type: none">HFMSE is a 33-item measure of motor function validated for SMA patients to assess daily living activities. Clinical trial had a total of six secondary end points including the following: percentage of SMA patients whose HFMSE scores increased of at least 3 points from baseline measurement, percentage of SMA patients who achieved a new World Health Organization motor milestone, a change in the Revised Upper Limb Module score from baseline.	Primary End Point Change from baseline HFMSE score, least-squares mean (95% CI) <ul style="list-style-type: none">Interim analysisFinal analysis Based on the interim analysis, results indicate a least square means increase from baseline to month 15. Thus, in the interim and final analysis there was a significant difference between the groups, favoring nusinersen.	Nusinersen Group N 84 4.0 (2.9 to 5.1) 3.9 (3.0 to 4.9)	Control Group 42 -1.9 (-3.8 to 0) -1.0 (-2.5 to 0.5)	Difference 5.9 (3.7 to 8.1) 4.9 (3.1 to 6.7)	P-Value 1

12. EMBRACE Clinical trial	1. Nusinersen (Spinraza®) <ul style="list-style-type: none">Dose was adjusted according to estimated cerebrospinal fluid for the infant's age on the day of dosingDoses for Part 1 were administered on days 1, 15, 29, 64,183, and 302Doses for Part 2 were administered on days 1, 120, 239, 358, 477, 596, and 715 2. Sham procedure (control group) <ul style="list-style-type: none">Procedure consisted of a small needle prick of a lumbar-puncture injection Sham procedures were administered on same dosing schedule as nusinersen treatment group	21	Study length: <ul style="list-style-type: none">Part 1(14 months)Part 2 (30 months)	Inclusion: <ul style="list-style-type: none">Confirmed diagnosis of SMA through genetic testing verifying 5q SMA (homozygous deletion, mutation, or compound heterozygote)One of the following:<ul style="list-style-type: none">Symptom onset ≤ 6 months of age and documentation of 3 copies of SMN2 geneSymptom onset ≤ 6 months of age, >7 months of age at screening, and documentation of 2 copies of SMN2 geneSymptom onset >6 months of age, ≤18 months of age at screening and documentation of 2 or 3 copies of the SMN2 geneFor part 2: participation in Part 1 and completion of the end of Part 1 evaluation assessments	Phase II two part study: Part 1 (DB, PC), Part 2 (OL extension study)	Primary outcome measures: <ul style="list-style-type: none">Number of participants experiencing adverse events and/or serious adverse eventsNumber of participants with the following clinically significant abnormalities: vital signs, weight, neurological examination, laboratory assessment, coagulation parameter, and electrocardiograms (ECGs).	<table><thead><tr><th>Primary End Point</th><th>Nusinersen Group (%)</th><th>Control Group(%)</th></tr><tr><th>N</th><th>21</th><th>NR</th></tr></thead><tbody><tr><td>Acute respiratory failure</td><td>8</td><td>NR</td></tr><tr><td>Pneumonia</td><td>14</td><td>NR</td></tr><tr><td>Respiratory distress</td><td>12</td><td>NR</td></tr><tr><td>Respiratory syncytial virus infection</td><td>6</td><td>NR</td></tr><tr><td>Respiratory tract infection</td><td>6</td><td>NR</td></tr><tr><td>Rhinovirus infection</td><td>8</td><td>NR</td></tr><tr><td>Respiratory failure</td><td>6</td><td>NR</td></tr></tbody></table> <p>Currently, due to the observed efficacy in the interim analysis of EMBRACE, the study was terminated early and patients were directly transitioned to the open-label extension. The progress report does not provide all primary outcome results; however, data regarding deaths and serious adverse events were made available.</p> <p>Nine patients reported 50 serious adverse events which were deemed unrelated to study treatment by the study investigators. One death occurred following hospitalization due to respiratory distress. As of now, data related to comparator group were unavailable.</p>	Primary End Point	Nusinersen Group (%)	Control Group(%)	N	21	NR	Acute respiratory failure	8	NR	Pneumonia	14	NR	Respiratory distress	12	NR	Respiratory syncytial virus infection	6	NR	Respiratory tract infection	6	NR	Rhinovirus infection	8	NR	Respiratory failure	6	NR
Primary End Point	Nusinersen Group (%)	Control Group(%)																																
N	21	NR																																
Acute respiratory failure	8	NR																																
Pneumonia	14	NR																																
Respiratory distress	12	NR																																
Respiratory syncytial virus infection	6	NR																																
Respiratory tract infection	6	NR																																
Rhinovirus infection	8	NR																																
Respiratory failure	6	NR																																
14. SHINE Clinical Trial	1. Nusinersen (Spinraza®)	292	Time frame: up to day 1,807	Inclusion: <ul style="list-style-type: none">Completion of index study in accordance of study protocol or as a result of sponsor decision	PA, Phase 3 clinical trial	Primary outcome measures: <ul style="list-style-type: none">Number of participants experiencing adverse events and/or serious adverse eventsNumber of participants with the following clinically significant abnormalities: vital signs, weight, neurological examination, laboratory assessment, coagulation parameter, and 12-lead electrocardiograms (ECGs).Change from baseline in concomitant medications <p>Number of secondary outcome measures submitted, since January 29,2019, were 23.</p>	Results: Pending Estimated final data collection for primary outcome measure is August 29, 2023																											

15. NURTURE Clinical Trial	1.Nusinersen	25	Time frame may go up to day 1,820 from baseline	Inclusion: <ul style="list-style-type: none"> Confirmed diagnosis of SMA through genetic testing verifying 5q SMA (homozygous deletion, mutation, or compound heterozygote) Genetic documentation of 2 or 3 copies of SMN2 Age ≤6 weeks at first dose 	SGA, OL	The primary objective of this study is to examine the efficacy of multiple doses of therapy administered intrathecally in presenting or delaying the need for respiratory intervention or death. Number of secondary outcome measures submitted, since April 20,2017, were 17	Results: Pending Estimated final data collection for primary outcome measure is January 25, 2022
Zolgensma® Clinical Trials							
13. START Clinical Trial, Zolgensma	Patients enrolled received an intravenous infusion of self-complementary adeno-associated viral serotype 9 (scAAV9) gene therapy <ul style="list-style-type: none"> Treatment arm 1: received a low dose (6.7x10¹³ vg/kg), these patients were enrolled from May 2014 through September 2014 Treatment arm 2: received a high dose (2.0x10¹⁴ vg/kg) and were enrolled from December 2014 through December 2015. 	15	Clinical trial time frame was depended upon treatment arm <ul style="list-style-type: none"> Treatment arm 1, low dose 4-5 months Treatment arm 2, high dose, about 1 year 	Inclusion: <ul style="list-style-type: none"> Confirmed diagnosis of SMA1, homozygous SMN1 exon 7 deletions, and two copies of SMN2 Baseline demographics <ul style="list-style-type: none"> Cohort 1 <ul style="list-style-type: none"> Mean age (6.3 months; range 5.9 to 7.2 months) Sex: 2 Female; 1 Male Race: 3 Caucasians Mean CHOP INTEND score: 16; range: 6-27) All patients had nutritional and ventilatory support at baseline Cohort 2 <ul style="list-style-type: none"> Mean age (3.4 months; range 0.9 to 7.9 months) Sex: 7 Female; 5 Male Race: 11 Caucasians; 1 Other Mean CHOP INTEND score: 28 (12-50) Patients that required clinical support at baseline: 5 nutritional support; 2 ventilatory support 	SGA, OL	Primary outcome measure: <ul style="list-style-type: none"> Determination of safety of any treatment-related adverse events of ≥ grade 3 (at least 16 hours of respiratory assistance per day for a minimum of 14 days in the absence of an acute, reversible illness, or perioperative state. Secondary outcome measure was the time until death or the need for permanent ventilatory assistance. Exploratory outcomes analysis included motor-milestone achievements and CHOP-INTEND scores	16 patients were screened and one was excluded due to persistent anti-AAV9 antibody titers. Survival and Permanent Ventilation As of August 7,2017 all enrolled patients reached a minimum age of 20 months and did not require permanent mechanical ventilation. Motor Function Assessments Patients, in both cohorts, had increased CHOP INTEND scores from baselines and maintained these changed. Cohort 1, low dose scAAV9, had a mean increase of 7.7 points from baseline. Cohort 2, high dose scAAV9, had a mean increase of 24.6 points from baseline. Safety Based on August's 7 th , 2017 update, there was a total of 56 serious adverse events that were observed in 13 patients. Of those adverse events reported, investigators confirmed 2 events, elevated alanine and aspartate aminotransferase (ALT, AST) above upper normal limit, were treatment-related grade 4 events through laboratory values.
16. STRIVE Clinical Trial Zolgensma	Onasemnogene Apeparvovec-xioi	20*	Time frame: 18 months of age vist	Inclusion: <ul style="list-style-type: none"> Confirmed diagnosis of SMA Type 1, gene mutation analysis with bi- 	SGA, OL	Primary outcome measures: <ul style="list-style-type: none"> Achievement of unassisted sitting for at least 30 seconds Event-free survival 	*=Estimated enrollment, 20 patients Results: Pending Estimated final data collection for primary outcome measure is December 12,2019

				allelic SMN1 mutations and 1 or 2 copies of SMN2 <ul style="list-style-type: none"> • Must be < 6 months of age at the time of treatment infusion 		Secondary outcomes include: ability to thrive and ventilatory support independence	
17. STRONG Clinical Trial Zolgensma	Treatment includes three different dosing of Onasemnogene abeparvovec-xioi: <ul style="list-style-type: none"> • Dose A: 6.0×10^{13} • Dose B: 1.2×10^{14} • Dose C: 2.4×10^{14} 	N/A	Time frame: up to 15 months from baseline			Primary outcome measures: <ul style="list-style-type: none"> • Incidence of adverse events • Determination of optimal dose • Patients ≥ 6 months and < 24 months standing milestone achievement • Patients ≥ 23 months and < 60 months change in HFMSE score from baseline Secondary outcomes include other motor milestone achievement and change from baseline in ventilation support	Results: Pending Clinical trial is actively recruiting, estimated primary completion date is June 1, 2021

Key: RCT=Randomized Controlled Trial; PC=Placebo Controlled; DB=Double Blinded; PA=Parallel Assignment; ITT=Intention-to-Treat; OL=Open-Label; SGA=Single Group Assignment

Summary and Recommendation

SMA is a debilitating neuromuscular disorder resulting from a defective SMN1 gene, which results in a range of phenotypes (type 0 – type 4). Affected patients require a multidisciplinary management that may include, pulmonologist, neuro-muscular rehabilitation, orthopedic, medication, acute care, etc.

Although SMA is severe disorder, research continues to advance and new treatment opportunities continue to emerge. This is seen with Spinraza®, first FDA approved SMA treatment, an antisense oligonucleotide designed to increase production of the deficient SMN protein. Spinraza® will be a lifelong therapy that will require maintenance dosing every 4 months. Clinical studies have demonstrated Spinraza®'s effectiveness; however long-term effectiveness is yet to be determined. As research continues to unfold for Spinraza, I recommend a prior authorization mirroring the package insert. Also, for reauthorization would recommend clinical chart notes documenting improvement since initiating therapy.

The newly approved SMA treatment, Zolgensma®, is a breakthrough gene therapy. Zolgensma® is designed to replace the defective SMN gene that will increase expression of the deficient protein. This therapy only requires a single intravenous infusion dose; however, this medication is also the most expensive therapy yet to market. Once again, long-term effectiveness is yet to be determined. Recommend creating a prior authorization mirroring the package insert along with a requirement of the specified monitoring period up to five months.

References

1. Bodamer A, O (2019). Spinal muscular atrophy. In J. F. Dashe (Ed.), *UpToDate*. Retrieved August 15, 2019 from <https://www.uptodate.com/contents/spinal-muscular-atrophy>
2. Spinal Muscular Atrophy. (n.d.) *Muscular Dystrophy Association*. Retrieved from <https://www.mda.org/disease/spinal-muscular-atrophy>
3. What is Spinal Muscular Atrophy. (n.d.) *SMA News Today*. Retrieved from <https://smanewstoday.com/what-is-spinal-muscular-atrophy/#>
4. SMA Life Expectancy and Disease Onset. (n.d.) *SMA News Today*. Retrieved from <https://smanewstoday.com/sma-life-expectancy/>
5. E. Mercuri, R.S. Finkel, F. Muntoni, et al. Diagnosis and management of spinal muscular atrophy: Part 1: recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. *Neuromuscul Disord*, 28 (2017), pp. 103-115, 10.1016/j.nmd.2017.11.005
6. R.S. Finkel, E. Mercuri, O.H. Meyer, et al. Diagnosis and management of spinal muscular atrophy. Part 2: pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. *Neuromuscul Disord*, 28 (2017), pp. 197-207, 10.1016/j.nmd.2017.11.004
7. Spinal Muscular Atrophy Treatment. (n.d.) *SMA News Today*. Retrieved from <https://smanewstoday.com/spinal-muscular-atrophy-treatment>
8. Spinraza® [package insert]. Cambridge, MA: Biogen; 2016.
9. Zolgensma® [package insert]. Bannockburn, IL: AveXis, Inc.; 2019.
10. Finkel, R. S. et al. Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy. *N Engl J Med* 377, 1723–1732, <https://doi.org/10.1056/NEJMoa1702752> (2017).
11. Mercuri, E. et al. Nusinersen versus Sham Control in Later-Onset Spinal Muscular Atrophy. *N Engl J Med* 378, 625–635, <https://doi.org/10.1056/NEJMoa1710504> (2018).
12. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 Feb 29. Identifier NCT02462759, A Study to Assess the Safety and Tolerability of Nusinersen (ISIS 396443) in Participants With Spinal Muscular Atrophy (SMA). (EMBRACE); 2015 Jun 4 [cited 2019 Aug 22]. Available from: <https://clinicaltrials.gov/ct2/show/record/NCT02462759?view=record>
13. Mendell, J. R. et al. Single-dose gene-replacement therapy for spinal muscular atrophy. *N. Engl. J. Med.* 377, 1713–1722 (2017).
14. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 Feb 29. Identifier NCT02594124, A Study for Participants With Spinal Muscular Atrophy (SMA) Who Previously Participated in Nusinersen (ISIS 396443) Investigational Studies. (SHINE); 2015 Nov 2 [cited 2019 Aug 24]. Available from: <https://clinicaltrials.gov/ct2/show/record/NCT02594124>
15. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 Feb 29. Identifier NCT02386553, A Study of Multiple Doses of Nusinersen (ISIS 396443) Delivered to Infants With Genetically Diagnosed and Presymptomatic Spinal Muscular Atrophy (NURTURE); 2015 Mar 12 [cited 2019 Aug 24]. Available from: <https://clinicaltrials.gov/ct2/show/record/NCT02386553>

16. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 Feb 29. Identifier NCT03306277, Gene Replacement Therapy Clinical Trial for Patients With Spinal Muscular Atrophy Type 1 (STRIVE); 2017 Oct 11 [cited 2019 Aug 24]. Available from: <https://clinicaltrials.gov/ct2/show/record/NCT03306277>
17. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 Feb 29. Identifier NCT03381729, Study of Intrathecal Administration of Onasemnogene Apeparvovec-xioi for Spinal Muscular Atrophy (STRONG); 2017 Dec 22 [cited 2019 Aug 24]. Available from: <https://clinicaltrials.gov/ct2/show/NCT03381729>